EDITORIAL

Is now the time for probiotics in diabetes management?

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Type 2 diabetes mellitus, a chronic progressive metabolic disease, has reached the proportions of an epidemic in the past 30 years, with worldwide prevalence approaching 400 million people. The epidemic is largely secondary to overnutrition and sedentary lifestyle, leading to highly prevalent overweight and obesity, which contribute to the development of type 2 diabetes.[1]

Patients with metabolic syndrome and abnormal fat distribution, with the expansion of visceral fat, have elevated plasma proinflammatory markers, prothrombotic state, and vascular dysfunction. These abnormalities contribute causally to the development of metabolic disorders observed in patients with central obesity.[2,3]

In recent years, considerable evidence has been gathered on the effect of gut microbiota composition as a potential factor affecting the energy balance and contributing to fat accumulation. The gut microbiota are one of the most important determinants of metabolic disorders such as obesity, insulin resistance, and type 2 diabetes with related comorbidities. There is an increasing number of studies exploring the effects of probiotic bacterial strains in the prevention or treatment of metabolic and cardiovascular risk factors.[4,5] The gut microbiota is affected by a complex interaction between the host's genetics and environment; however, diet is one of the main factors affecting intestinal bacterial composition.

The "western" diet, rich in saturated/trans fats and simple sugars and poor in fibers, is associated with the alteration of bacterial population, leading to disruption of intestinal barrier, activation of proinflammatory mechanisms, and metabolic endotoxemia. In consequence, this leads to excessive internal diffusion of bacterial fragments/products, which promotes inflammation in key insulin-responsive tissues, resulting in insulin resistance.[6-8]

There are several approaches to modifying the colonic flora and manipulating the intestinal microbiota, namely, the use of prebiotics, probiotics, and fecal microbial transplants.[4,5,7,8]

Prebiotics are defined as a selectively fermented ingredients that result in specific changes to the composition and activity of the gastrointestinal microbiota, and mainly increase the number of bifidobacteria, thus conferring a health benefit on the host. Prebiotics are nondigestible polysaccharides that promote the production of short-chain fatty acids and the growth of beneficial gut bacteria, especially Bifidobacterium and Lactobacillus. Substrates accepted as prebiotics include fructans (inulin) and fructo-oligosaccharides, galacto-oligosaccharides, and lactulose. Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Most currently used probiotics belong to bifidobacteria, lactic acid bacteria, most of them phylum Firmicutes, dairy propionibacteria, yeasts (*Saccharomyces boulardii*), *Bacillus*, and the gram-negative *Escherichia coli* strain Nissle 1917.[6-8]

The dietary prebiotics affect total energy intake, body weight, peptide YY and glucagon-like peptide-1 concentrations, gastric emptying times, insulin sensitivity, lipids, and inflammatory markers and immune function, although their effects were contradictory. Dietary prebiotic consumption was found to be associated with subjective improvements in satiety and reductions in postprandial glucose and insulin concentrations.[4,5,9]

Probiotic treatment aiming at modifying the colonic flora is thought to produce benefit for several reasons: 1) the intestinal bacterial flora favors the digestion and absorption of nutrients; 2) gut microbiota is related to overall immunity of the host; and 3) microbiome may alter the synthesis of intestinal hormones such as glucagon-like peptide 1 and influences the host metabolism.[4,5,8,10,11]

Probiotics are able to decrease metabolic endotoxemia by restoring the disrupted intestinal mucosal barrier. There is the perspective of using new bacterial strains, such as butyrate-producing

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bacteria and the mucolytic *Akkermansia muciniphila*, as well as prebiotics to enhance the functionality of probiotics.

In the current issue of *Pol Arch Med Wewn*, Kasińska and Drzewoski,[12] in their article, assessed the effect of probiotic supplementation on selected modifiable cardiometabolic risk factors in type 2 diabetes by a meta-analysis of existing research. The authors carefully planned the material included in the meta-analysis (reviewed articles in PubMed, Embase, Cochrane Library, and Scopus databases and searched the databases using the terms "probiotics" and "diabetes"). They included only full-text articles published in English on randomized controlled trials (RCTs) including adult patients with diagnosed type 2 diabetes. Eventually, 8 RCTs involving 438 subjects were included in the meta-analysis.

A pooled analysis of 3 RCTs showed a significant decrease in the level of hemoglobin A_{1c} (HbA_{1c}) in diabetic patients consuming probiotics compared with those consuming placebo (standardized mean difference [SDM], –0.81; confidence interval [CI], –1.33 to –0.29; $P = 0.0021$) and also 3 RCTs demonstrated a significant decrease of HOMA-IR after consumption of probiotics vs placebo (SMD, –2.10; CI, –3.00 to –1.2, $P < 0.0001$; $I^2 = 82.91\%$; $P = 0.0029$ for heterogeneity). In the meta-analysis, supplementation with probiotics was not found to alter the lipid profile or the levels of fasting glucose, insulin, or C-reactive protein.

Overall, the results of the meta-analysis are important for the treatment of patients with type 2 diabetes. The use of probiotics has been shown to significantly improve long-term glycemic control, measured by HbA_{1c} levels and insulin resistance, assessed by the HOMA-IR. These effects could potentially inhibit the progression of the disease and hamper the development of its chronic complications. Finally, the use of well-studied probiotic species is safe, and they are generally well tolerated.[13]

A meta-analysis allows to combine individual small trials to improve the power to detect the direction, size, and consistency of an effect. It is necessary to use a meta-analysis to synthesize the results of RCTs into recommendations for clinicians. The results of this meta-analysis are important for the treatment of diabetes and prevention of macro- and microvascular complications. However, the main limitation of this meta-analysis is a lack of subgroup analysis for specific species/strains or species combination on metabolic parameters. The different probiotic species/strains used in clinical trials in different doses will likely affect their clinical efficacy in type 2 diabetes patients. Therefore, synthesizing the data from different interventions may in part be responsible for the significant heterogeneity observed in the current meta-analysis. Some authors recommend that all future meta-analyses of probiotics, in any clinical setting, should include subgroup analyses on specific species/strains and specific combinations.[14]

Metabolic disorders, such as obesity, diabetes, and cardiovascular disease, are widespread in industrialized societies. The concept that manipulating the gut microbiota, which influences metabolic diseases to improve host metabolism, has gained a considerable interest in recent years. Currently, several potential bacterial species have been identified, and novel mechanisms of action influencing their beneficial effects have been elucidated. The new treatment option is incorporation of genetically modified bacteria that secrete molecules into the intestinal microbiota to provide sustained treatment. The genetically modified bacteria are capable of producing sufficient amounts of secreted small molecules to induce significant therapeutic effects on the target organ outside the intestinal tract.[15]

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